Box 1. Glossary

Adenoma: A benign tumor composed of epithelial cells.

Alternative lengthening of telomeres (ALT): A process of maintaining telomeres independent of telomerase, the enzyme normally responsible for telomere replication.

Amplification: A genetic alteration producing a large number of copies of a small segment (less than a few megabases) of the genome.

Angiogenesis: the process of forming vascular conduits, including veins, arteries, and lymphatics.

Benign tumor: An abnormal proliferation of cells driven by at least one mutation in an oncogene or tumor suppressor gene. These cells are not invasive (i.e., they cannot penetrate the basement membrane lining them), which distinguishes them from malignant cells.

Carcinoma: A type of malignant tumor composed of epithelial cells.

Clonal mutation: A mutation that exists in the vast majority of the neoplastic cells within a tumor.

Driver gene mutation (driver): A mutation that directly or indirectly confers a selective growth advantage to the cell in which it occurs.

Driver gene: A gene that contains driver gene mutations (Mut-Driver gene) or is expressed aberrantly in a fashion that confers a selective growth advantage (Epi-Driver gene).

Epi-driver gene: A gene that is expressed aberrantly in cancers in a fashion that confers a selective growth advantage.

Epigenetic: Changes in gene expression or cellular phenotype caused by mechanisms other than changes in the DNA sequence.

Exome: The collection of exons in the human genome. Exome sequencing generally refers to the collection of exons that encode proteins.

Gatekeeper: A gene that, when mutated, initiates tumorigenesis. Examples include *RB*, mutations of which initiate retinoblastomas, and *VHL*, whose mutations initiate renal cell carcinomas.

Germline genome: An individual's genome, as inherited from their parents.

Germline variants: Variations in sequences observed in different individuals. Two randomly chosen individuals differ by ~20,000 genetic variations distributed throughout the exome.

Human leukocyte antigen (HLA): A protein encoded by genes that determine an individual's capacity to respond to specific antigens or reject transplants from other individuals.

Homozygous deletion: Deletion of both copies of a gene segment (the one inherited from the mother, as well as that inherited from the father).

Indel: A mutation due to small insertion or deletion of one or a few nucleotides.

Karyotype: Display of the chromosomes of a cell on a microscopic slide, used to evaluate changes in chromosome number as well as structural alterations of chromosomes.

Kinase: A protein that catalyzes the addition of phosphate groups to other molecules, such as proteins or lipids. These proteins are essential to nearly all signal transduction pathways.

Liquid tumors: Tumors composed of hematopoietic (blood) cells, such as leukemias. Though lymphomas generally form solid masses in lymph nodes, they are often classified as liquid tumors because of their derivation from hematopoietic cells and ability to travel through lymphatics.

Malignant tumor: An abnormal proliferation of cells driven by mutations in oncogenes or tumor suppressor genes that has already invaded their surrounding stroma. It is impossible to distinguish an isolated benign tumor cell from an isolated malignant tumor cell. This distinction can be made only through examination of tissue architecture.

Metastatic tumor: A malignant tumor that has migrated away from its primary site, such as to draining lymph nodes or another organ.

Methylation: Covalent addition of a methyl group to a protein, DNA, or other molecule.

Missense mutation: A single-nucleotide substitution (e.g., C to T) that results in an amino acid substitution (e.g., histidine to arginine).

Mut-driver gene: A gene that contains driver gene mutations.

Nonsense mutation: A single-nucleotide substitution (e.g., C to T) that results in the production of a stop codon.

Nonsynonymous mutation: A mutation that alters the encoded amino acid sequence of a protein. These include missense, nonsense, splice site, translation start, translation stop, and indel mutations.

Oncogene: A gene that, when activated by mutation, increases the selective growth advantage of the cell in which it resides.

Passenger mutation (passenger): A mutation that has no direct or indirect effect on the selective growth advantage of the cell in which it occurred.

Primary tumor: The original tumor at the site where tumor growth was initiated. This can be defined for solid tumors, but not for liquid tumors.

Promoter: A region within or near the gene that helps regulate its expression.

Rearrangement: A mutation that juxtaposes nucleotides that are normally separated, such as those on two different chromosomes.

Selective growth advantage (*s*): The difference between birth and death in a cell population. In normal adult cells in the absence of injury, $s = 0.000000$.

Self-renewing tissues: Tissues whose cells normally repopulate themselves, such as those lining the gastrointestinal or urogenital tracts, as well as blood cells.

Single-base substitution (SBS): A single-nucleotide substitution (e.g., C to T) relative to a reference sequence or, in the case of somatic mutations, relative to the germline genome of the person with a tumor.

Solid tumors: Tumors that form discrete masses, such as carcinomas or sarcomas.

Somatic mutations: Mutations that occur in any non–germ cell of the body after conception, such as those that initiate tumorigenesis.

Splice sites: Small regions of genes that are juxtaposed to the exons and direct exon splicing.

Stem cell: An immortal cell that can repopulate a particular cell type.

Subclonal mutation: A mutation that exists in only a subset of the neoplastic cells within a tumor.

Translocation: A specific type of rearrangement where regions from two nonhomologous chromosomes are joined.

Tumor suppressor gene: A gene that, when inactivated by mutation, increases the selective growth advantage of the cell in which it resides.

Untranslated regions: Regions within the exons at the 5′ and 3′ ends of the gene that do not encode amino acids.